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EXAMINER	
GOON, SCARLETT Y	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,587	ROSENBERG ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38 and 40-71* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,9,19,21,32-38,40,42,44,49-62,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,10-18,20,22-31,43,45-48,63 and 66-71* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 December 2009 has been entered.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 23 December 2009 in which claim 39 is cancelled, claims 1, 2, 6, 11, 12, 45 and 63 are amended to change the scope and breadth of the claims, and new claims 66-71 are added.

Claims 1-38 and 40-71 are pending in the instant application.

Claims 3-5, 19, 21, 32-38, 40, 41, 49-62, 64 and 65 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 7, 9, 42 and 44 are withdrawn from further consideration in the Office Action dated 15 September 2009 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2, 6, 8, 10-18, 20, 22-31, 43, 45-48, 63 and 66-71 are examined on its merits herein.

Priority

This application claims priority to U.S. provisional application no. 60/429,946 filed on 27 November 2002 and U.S. provisional application no. 60/456,889 filed on 21 March 2003.

Rejections Withdrawn

In view of the cancellation of claim 39, all rejections made with respect to claim 39 in the previous Office Action are withdrawn.

Claim Objections

Claims 1 and 2 are objected to because of the following informalities: The article "[a]n" at the beginning of the claims should be corrected to "a" in order to be grammatically correct. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Section [0001]

Claims 1, 2, 8, 10, 13-17, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Pikas (IDS dated 26 December 2006).

Pikas teaches enzymes involved in the biosynthesis and degradation of heparin-related polysaccharides, namely heparanase, which degrades heparin and heparan sulfate, and N-deacetylase/N-sulfotransferase (NDST), which generates the complex structure of heparin and heparan sulfate. In determining the substrate recognition properties of heparanase, Pikas modified a polysaccharide obtained from the K5 strain of *Escherichia coli* having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ (p. 306, column 1, C-2). This K5 polysaccharide is identical to the unmodified parts of heparin sulfate. The K5 polysaccharide was modified in a controlled stepwise fashion by combining different treatments; (1) chemical *N*-deacetylation and *N*-sulfation, (2) enzymatic GlcA C5-epimerization and (3) chemical O-sulfation.

Thus, the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$, obtained from the K5 strain of *Escherichia coli*, by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical O-sulfation, disclosed by Pikas, anticipates claims 1, 2, 8, 10, 13-17, 67 and 68.

Response to Arguments

Applicants' arguments, filed 23 December 2009, with respect to the rejection of claims 1, 2, 8, 10 and 13-17 made under 35 USC § 102(b) as being anticipated by Pikas, have been fully considered but they are not persuasive.

Applicants argue that the claims have been amended to recite that the method described therein is enzymatic only and in contrast to that, Pikas discloses a method that involves chemical steps. These arguments are not persuasive because the claims use the transitional phrase "comprising". The transitional terms "comprising" and “characterized by” are open-ended and does not exclude additional, unrecited elements or method steps. Thus, although Applicants have amended the claims to recite that the method is enzymatic only, the use of “comprising” language does not exclude the addition of chemical steps.

The rejection is still deemed proper and therefore adhered to.

Section [0002]

Claims 1, 2, 6, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Toida *et al.* (PTO-892, Ref. U).

Toida *et al.* disclose the enzymatic preparation of heparin oligosaccharides containing antithrombin III binding sites. Heparin (10 g) was prepared in 200 mL of 250 mM calcium acetate, 2.5 mM sodium acetate, 1 mM Tris, pH 7.10, and filter sterilized (p. 32041, column 2, first full paragraph). The reaction was carried out at 30 °C, and heparin lyase I was added at three different intervals. After the reaction reached 10% digestion in 96 h, the mixture was removed from the water bath and heated to 100 °C for 2 min. The resultant oligosaccharides were fractionated by gel permeation chromatography. The hexasaccharide, octasaccharide and decasaccharide fractions, expected to contain intact pentasaccharide ATIII-binding sites were collected, desalted

and then freeze-dried (p. 32043, column 1, last paragraph). The various fractions were purified to homogeneity on a SAX-HPLC. The oligosaccharides contained intact binding sites at a high level of purity, and exhibited the expected affinity toward ATIII and anticoagulant activity (p. 32046, column 2, last paragraph).

Thus, the enzymatic preparation of heparin oligosaccharides by treating porcine mucosal heparin with heparin lyase, disclosed by Toida *et al.*, anticipate claims 1, 2, 6, 8 and 10.

Section [0003]

Claims 1, 2, 6-10, 13-17, 67 and 68 are rejected under 35 U.S.C. 102(b) as being anticipated by journal publication by Wei *et al.* (of record).

Wei *et al.* disclose that the biosynthesis of heparin sulfate utilizes a single protein that possesses both *N*-deacetylase and *N*-sulfotransferase activities (abstract). Towards characterizing the activity of the *N*-deacetylase, the release of [^{3}H]acetate from *N*-[^{3}H]acetylated polysaccharide derived from *Escherichia coli* K5 was measured (p. 3886, column 1, first paragraph).

It is noted that Wei *et al.* do not disclose the amount of sulfates present in the *Escherichia coli* K5 polysaccharide. However, as evidenced by Vann *et al.* (of record), the capsular polysaccharide from *Escherichia coli* 010:K5:H4 is a repeating disaccharide unit comprising 4-β-glucuronyl-1,4-α-N-acetylglucosaminyl residues (abstract) that is similar to that of desulfo-heparin (p. 363, column 1, paragraphs 2 and

3). Wei *et al.* indicate that heparan sulfate and heparin only differ in sulfate content and iduronic acid content (p. 3888, column 1, first full paragraph).

Thus, the assay used in characterizing *N*-deacetylase activity, wherein an acetate residue is removed from the *N*-acetylated polysaccharide of *Escherichia coli* K5, anticipates the method of preparing a sulfated polysaccharide in claims 1, 2, 6-10, 13-17, 67 and 68.

Response to Arguments

Applicants' arguments, filed 23 December 2009, with respect to the rejection of claims 1, 2, 6-10 and 13-17 made under 35 USC § 102(b) as being anticipated by Wei *et al.*, have been fully considered but they are not persuasive.

Applicants argue that the Wei *et al.* reference does not teach that the sulfated polysaccharide is capable of binding to a protein, as recited in the instant claim amendments. Applicants further argue that Wei *et al.* only teach one step in the sulfation of a polysaccharide, the N-deacetylation-N-sulfation of the N-position of the glycosidic structure, and that this incompletely sulfated polysaccharide is unable to bind to proteins known in the art. Applicants cite the teachings of Wei *et al.* that the "formation of these protein-binding domains in heparin sulfate is dependent on a series of biosynthetic reactions that modify the polysaccharide backbone," and that N-deacetylation-N-sulfation is just the first step. These arguments are not persuasive because the product obtained from *N*-deacetylation/*N*-sulfation can be recognized by a GlcA C5-epimerase, which is a protein that catalyzes the conversion of the glucuronic

acid residue of a heparin/heparan sulfate structure into iduronic acid. As disclosed by Habuchi *et al.*, the glucuronyl C5-epimerase requires preceding N-sulfation of the neighboring *N*-acetylglucosamine for catalysis of GlcA to IdoA (p. 69-70, section E-1). Alternatively, the resulting product can be recognized by heparitinase I, a protein, which Nader *et al.* teach as acting on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate. Applicants' argument appears to limit sulfated polysaccharide binding to only those proteins that recognize the fully modified heparan sulfate structure. However, this limitation is not recited in the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The rejection is still deemed proper and therefore adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0004]

Claims 6, 11, 12, 18, 20, 22-31, 46, 47, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Pikas (IDS dated 26 December 2006), as applied to claims 1, 2, 8, 10, 13-17, 67 and 68 above, further in view of journal publication by Habuchi *et al.* (of record), in view of journal publication by Koeller (PTO-892, Ref. V), in view of journal publication by Toone *et al.* (PTO-892, Ref. W).

The teachings of Pikas were as disclosed above in section [0001] of the claim rejections uncer 35 USC § 102.

The teachings of Pikas differ from that of the instantly claimed invention in that O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.

Habuchi *et al.* teach that various enzymes participating in the biosynthesis of heparan sulfate have been purified to homogeneity and cloned (p. 65, paragraph 2). Studies of the heparan sulfate enzymes offered new information regarding the specificity of the enzymes, and further confirmed the biosynthetic process as depicted in Figure 1. (p. 69). As indicated, the biosynthesis of heparan sulfate depends on multiple glycotransferases, sulfotransferases, and an epimerase. Most of these enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, including *N*-deacetylase/*N*-sulfotransferases, 3-*O*-sulfotransferases, 6-*O*-sulfotransferses, a 2-*O*-sulfotransferase, and an epimerase (entire article). *N*-deacetylase/*N*-sulfotransferase is a bifunctional enzyme responsible for N-deacylating the GlcNAc unit followed by *N*-sulfation of the resulting amino group (p. 70-72, section E-2-1). Enzymes of this subfamily differ in the extent of *N*-sulfation. The 3-*O*-sulfotransferases, 6-*O*-sulfotransferases and 2-*O*-sulfotransferase catalyze the transfer of a sulfate group from PAPS to the corresponding position on the heparin chain. Although the 2-*O*-sulfotransferase generally only catalyzes the transfer of a sulfate group to C-2 of an iduronic acid residue, C-2 sulfation of GlcA may occur during a transient period after *N*-deacetylation/*N*-sulfation of GlcNAc and before epimerization of GlcA (p. 74, first full paragraph). Glucuronyl C5-epimerase catalyzes the conversion of D-glucuronic acid to L-iduronic acid units (p. 69-70, section E-1). The glucuronyl C5-epimerase requires preceding *N*-sulfation of the neighboring *N*-acetylglucosamine.

Koeller *et al.* teach complex carbohydrate synthesis tools for glycobiologists. Complex carbohydrate and glycoconjugate synthesis, such as of the heparin

pentasaccharide repeating unit for anti-coagulant acitivty (Figure 1), remains much more complicated than that of other biomolecules (p. 1158, column 1, first paragraph). However, enzyme-based strategies toward complex glycoconjugates are an emerging technology that has the great potential to greatly simplify glycan assembly. Koeller *et al.* teach that the application of enzymes to organic synthesis is a particularly powerful approach, and in some cases a single enzymatic transformation can be substituted in place of numerous sequential chemical reactions (p. 1158, paragraph bridging two columns). In the case of complex oligosaccharide synthesis, the enzymatic approach is especially noteworthy for glycosidic bond formation. Such enzymatic techniques have greatly simplified the synthesis of carbohydrate-based structures and enzymatic methods will gain increased utility as more glycosyltransferases become available and substrate cost decreases (p. 1167, column 1). Koeller *et al.* further teach that post-translational modifications, such as sulfation, phosphorylation, and esterification, are also important additions to glycoconjugate structure (p. 1167, column 1). Future progress in glycobiology will be greatly aided by techniques, such as the disclosed enzymatic synthesis method, that allow facile synthetic access to specific glycoconjugates.

Toone *et al.* teach use of enzymes as catalysts in carbohydrate synthesis. Enzymes offer two major advantages over classical methodologies for the synthesis of carohydrates (p. 2, first incomplete paragraph). First, enzymes are compatible with aqueous media, which is the most practical medium for synthetic manipulations of unprotected, hydrophilic compounds such as carbohydrates, and therefore avoids the

necessity for protection/deprotection schemes (p. 2, first full paragraph). Second, enzyme-catalyzed reactions demonstrate absolute chemospecificity, regiospecificity, and stereospecificity, which is important because carbohydrates generally contain a number of hydroxyl groups of approximately equal reactivity (p. 2, second full paragraph). Therefore, the ability to selectively manipulate a single hydroxyl residue is clearly important.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis. Since Habuchi *et al.* teach that many of the enzymes that participate in heparan sulfate biosynthesis have been purified and molecularly cloned, and that their substrate specificities have been characterized, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the chemical modification steps for modification of the polysaccharide disclosed in Pikas (chemical *N*-deacetylation and *N*-sulfation and chemical *O*-sulfation), with enzymatic steps using the enzymes disclosed by Habuchi *et al.* Since Koeller *et al.* teach that the chemical synthesis of complex carbohydrates, such as heparin, is complicated, and that

a single enzymatic transformation can be substituted in place of numerous sequential chemical reactions, one would have been motivated to combine the teachings and substitute enzymatic modifications in place of the chemical modifications. Furthermore, as Koeller *et al.* teach that post-translation modification, such as sulfation or phosphorylation are important additions to glycoconjugate structure, one of ordinary skill in the art would have been motivated to use the sulfotransferase enzymes dislcosed by Habuchi *et al.* in place of the chemical method disclosed by Pikas *et al.*, in order to receive the expected benefit, as disclosed by Toone *et al.*, that the use of enzymes in carbohydrate synthesis is advantageous over classifical methods because enzyme-catalyzed reactions demonstrate absolute chemospecificity, regiospecificity, and stereospecificity, therefore avoiding the necessity for protection/deprotection schemes. In other words, the use of enzymes allows one to have better control over the generated product.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 23 December 2009, with respect to the rejection of claims 6, 11, 12, 18, 20, 22-31, 46 and 47 made under 35 USC § 103(a) as being unpatentable over Pikas, as applied to claims 1, 2, 8, 10 and 13-17, further in view of journal publication by Esko *et al.*, have been fully considered but are moot in view of the new/modified ground(s) of rejection applied above.

Insofar as Applicants' arguments are still applicable to the instant rejection, Applicants' argue that neither Pikas or Esko *et al.*, nor their combination, teach or suggest every limitation of the present claims because one of ordinary skill would have had no motivation to combine the process of Pikas with the process of Esko, and therefore would have had no reasonable expectation of success for the presently claimed methods based on such a combination. Applicants further argue that the Examiner has provided no comments or arguments of any kind to substantiate the blanket statement that the use of enzymes "allows one to sulfate only specific sites…allowing one to have better control over the generated product" or that "it is well known…that the use of enzymes results in a defined product as enzymes are generally substrate specific." Thus, Applicants argue that these statements could have only been made in hindsight. These arguments are not persuasive in view of the new/modified ground of rejection applied above. Specifically, the teachings of Koeller *et al.* and Toone *et al.* teach that enzymatic reactions are advantageous over chemical reactions with regards to carbohydrates because of their simplicity as compared to multi-step chemical reactions, and their chemospecificity, regiospecificity, and stereospecificity.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as described in the new/modified grounds of rejection above.

Section [0005]

Claims 43, 45, 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by Pikas (IDS dated 26 December 2006), as applied to claims 1,

2, 8, 10, 13-17, 67 and 68, further in view of journal publication by Habuchi *et al.* (of record), in view of journal publication by Koeller*et al.* (PTO-892, Ref. V), in view of journal publication by Toone *et al.* (PTO-892, Ref. W), as applied to claims 6, 11, 12, 18, 20, 22-31, 46, 47, 69 and 70, further in view of journal publication by van Boeckel *et al.* (PTO-892, Ref. X), in view of journal publication by Kushe *et al.* (of record),), in view of journal publication by Nader *et al.* (of record), in view of journal publication by Myette *et al.* (of record).

The teachings of Pikas were as disclosed in section [0001] above of the claim rejections under 35 USC § 102. The teachings of Habuchi *et al.*, Koeller *et al.*, and Toone *et al.* were as disclosed above in section [0004] of the claim rejections under 35 USC § 103.

The combined teachings of Pikas, Habuchi *et al.*, Koeller *et al.*, and Toone *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art do not disclose the use of heparitinase or $\Delta^{4,5}$ unsaturated glycuronidase in the synthesis of heparan sulfate compounds.

Van Boeckel *et al.* teach the unique antithrombin III binding domain of heparin is a lead to new synthetic antithrombotics. Since the ability of heparin fragments to reinforce ATIII-mediated inhibition of factor Xa appeared independent of their size, it was logical to look for the smallest fragments able to catalyze inhibition of factor Xa (p. 1673, column 2, section 2.2). An evaluation of different heparin sulfate fragments suggested that the pentasaccharide sequence DEFGH (Figure 1, p. 1672) is the active sequence (p. 1673, column 2, section 2.2). Van Boeckel *et al.* teach that since no

biochemical tool for further controlled degradation was available at the time to obtain pentasaccharide DEFGH from CDEFGH (structure 4 of Figure 1, p. 1672), chemical synthesis was required (p. 1674, column 1, first full paragraph).

Kusche *et al.* teach the biosynthesis of heparin. Extensive studies have elucidated the sequence of effects occurring during the biosynthesis of heparin and heparan sulfate (p. 7401, column 1, first incomplete paragraph). In the presence of UDP-GlcNAc and UDP-GlcA, a nonsulfated polysaccharide ($(GlcA\text{-}GlcNAc)_n$) is formed that is covalently linked to a protein core in a proteoglycan structure. Upon addition of the sulfate donor PAPS, a series of modifications take place, beginning with deacetylation and N-sulfation of the GlcNAc units. The latter reaction creates the proper substrate structure for C-5 epimerization of GlcA to IdoA units, and the assembly process is then concluded by stepwise O-sulfation in several positions (C-2 of IdoA and C-2 or C-3 of GlcA units, C-3 and C-6 of GlcN units). The polysaccharide chains of heparin and heparan sulfate display extensive structural variability, with potential for specific interaction with other macromolecules via the presence of unique sequences (p. 7400, column 2, paragraph 1). One such interaction is the antithrombin-binding region, essential for the blood anticoagulant activity of heparin. The structure of the antithrombin-binding region is shown in Figure 1 (p. 7401, column 1). Kushe *et al.* further teach the various substituents of heparin that are important for antithrombin binding. The structure of the pentasacharide sequence is largely nonvariable and cannot be modified without dramatic loss of biological activity (p. 7400, column 2, paragraph 1). As indicated, the 3-*O*-sulfate group of unit III is essential for the high

affinity binding of heparin to antithrombin and is a marker component of the antithrombin-binding region (Fig. 1 legend). The 6-*O*-sulfate group of unit I and the N-sulfate groups of units III and V are also critically important for antithrombin binding. The modification of the amino group of unit I with either an acetate or sulfate group does not affect antithrombin binding. Additionally, the sulfate groups at C-2 and C-6 of units IV and V, respectively, are less essential for antithrombin binding.

Nader *et al.* teach the purification and substrate specificity of heparitinase I and heparitinase II from *Flavobacterium heparinum*. These enzymes are responsible for the degradation of glycosaminoglycans. Heparitinase I acts on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate (abstract). Heparitinase II acts preferentially upon *N*-6-sulfated and/or *N*-acetylated, 6-sulfated glucosaminido-α-1,4-glucuronic acid linkages (p. 16813, column 1, last paragraph).

Myette *et al.* teach the cloning and substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase from *Flavobacterium heparinum*. This enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides that result from prior heparinase (and heparitinase) eliminative cleavage (abstract). It discriminates both on the basis of glycosidic linkage and sulfation pattern (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate

specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis, with the teachings of van Boeckel *et al.*, regarding the synthesis of the pentasaccharide sequence DEFGH as an antithrombotic, with the teachings of Kusche *et al.*, regarding the sequence of events involved in the biosynthesis of heparin and heparan sulfate and the various substituents of heparin that are important for antithrombin binding, with the teachings of Nader *et al.*, regarding heparitinase enzymes which are responsible for the degradation of glycosaminoglycans, with the teachings of Myette *et al.*, regarding the substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase.

Since van Boeckel *et al.* teach that the pentasaccharide sequence DEFGH is the smallest fragment able to catalyze inhibition of factor Xa and may therefore be useful as an antithrombotic, and Kusche *et al.* teach the importance of the various substituents on the pentasaccharide that are important for antithrombin binding, one of ordinary skill in the art would have been motivated to degrade the polysaccharide chain obtained from *E. coli* K5, as disclosed in Pikas *et al.*, into smaller fragments, more specifically, into the pentasaccharide disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombin III activity. As the teachings of Koeller *et al.* and Toone *et al.* indicate that modification and/or synthesis of carbohydrates are advantageously accomplished by the use of enzymes, one of ordinary skill in the art would have been motivated to look to the different enzymes that could be used in the synthesis of the pentasaccharide

fragment. As Toone *et al.* teach that enzymes have chemospecificity, regiospecificity, and stereospecificity, and Kusche *et al.* teach the biosynthetic sequence of events for the synthesis of heparin and heparan sulfate, one of ordinary skill in the art would have been motivated to model their order of enzymatic synthetic reactions after the biosynthetic pathway, in order to receive the expected benefit that following the biosynthetic sequence would maintain the specificities of the enzymes. However, as the K5 polysaccharide must also be degraded into the pentasaccharide fragment, one of ordinary skill in the art would also have to take into account the substrate specificities of these additional enzymes and insert them appropriately into the reaction scheme so as to maintain specificity of all the enzymes necessary for conversion of the *E. coli* K5 polysaccharide, disclosed by Pikas, into the pentasaccharide sequence disclosed by Kusche *et al.* Since the enzyme specificities for heparitinase, used for degradation of the large polymer into smaller saccharide units, is disclosed by Nader *et al.*, and the enzyme specificities of heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, used for removal of the $\Delta^{4,5}$ unsaturated glycosyl residue resulting from heparitinase digestion, is disclosed by Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to insert their use appropriately into the heparin/heparan sulfate reaction scheme depending on the required substrate specificities of these additional enzymes.

Thus, as the combined teachings of the prior art teach that pentasaccharide DEFGH, as disclosed by van Boeckel *et al.* and Kusche *et al.*, may be useful as an antithrombotic, one of ordinary skill in the art would have been motivated to synthesize such a compound. Since Koeller *et al.* and Toone *et al.* teach that enzymatic reactions

of carbohydrates are advantageous over traditional chemical synthetic methods, one of ordinary skill in the art would have been motivated to identify enzymes useful in the synthesis of heparin/heparin sulfate. As Kushe *et al.* disclose the biosynthetic scheme for the synthesis of heparin/heparin sulfate, and the purified enzymes are readily available and their substrate specificities are known, as taught by Habuchi *et al.*, Nader *et al.* and Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to use these enzymes, in accordance with their known substrate specificities, to enzymatically synthesize the pentasaccharide sequence disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombotic activity. It is noted that several different enzymatic synthetic sequences could result even after taking into account the different substrate specificities of the individual enzymes involved. However, Applicants are requested to note that it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious results. See MPEP § 2144.04. *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959); *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930); *Cohn v. Comr. Patents*, 251 F. Supp. 437, 148 USPQ 486 (D.C. 1966).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 23 December 2009, with respect to the rejection of claims 39, 43, 45, 48 and 63 made under 35 USC § 103(a) as being unpatentable over Pikas, as applied to claims 1, 2, 8, 10 and 13-17, further in view of journal publication by Kusche *et al.*, in view of journal publication by Habuchi *et al.*, in view of journal publication by Nader *et al.*, in view of journal publication by Myette *et al.*, have been fully considered but are moot in view of the new/modified ground(s) of rejection applied above.

Applicants' argue that the teachings of Kusche *et al.*, Habuchi *et al.*, Nader *et al.*, and Myette *et al.*, do not cure the deficiencies of Pikas, which teaches a combination of chemical and enzymatic synthetic steps, because none of the additionally cited prior art disclose or suggest any *in vitro*, enzymatic only method for synthesizing heparin sulfate or a sulfated polysaccharide capable of binding to a protein, as required by the present claims. Insofar as Applicants' arguments are still applicable to the instant rejection above, this argument is not persuasive because the teachings of Koeller *et al.* and Toone *et al.* expressly indicate that enzymatic reactions are advantageous over chemical reactions with regards to carbohydrates because of their simplicity as compared to multi-step chemical reactions, and their chemospecificity, regiospecificity, and stereospecificity. Thus, in view of the cloned enzymes involved in the heparin/heparan sulfate biosynthetic pathway, and the characterization of their substrate specificities, one of ordinary skill in the art would have been motivated to substitute the chemical reactions disclosed by Pikas with enzymes known in the art.

Furthermore, as indicated in the new/modified ground of rejection above, van Boeckel *et al.* and Kusche *et al.* teach that the pentasaccharide could be useful as an antithrombotic, thereby motivating one to synthesize such a compound using methods disclosed in the combined teachings of the prior art.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as described in the new/modified grounds of rejection above.

Section [0006]

Claims 63, 66 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over journal publication by van Boeckel *et al.* (PTO-892, Ref. X), in view of journal publication by Kushe *et al.* (of record), in view of journal publication by Pikas (IDS dated 26 December 2006), in view of journal publication by Habuchi *et al.* (PTO-892, of record), in view of journal publication by Nader *et al.* (of record), in view of journal publication by Myette *et al.* (of record), in view of journal publication by Koeller *et al.* (PTO-892, Ref. V), in view of journal publication by Toone *et al.* (PTO-892, Ref. W).

The teachings of van Boeckel *et al.* were as disclosed above in section [0005] of the claim rejections under 35 USC § 103.

The teachings of van Boeckel *et al.* differ from that of the instantly claimed invention in that van Boeckel *et al.* do not disclose synthesis of the ATIII-binding pentsaccharide by enzymatic methods.

The teachings of Kusche *et al.* were as disclosed above in section [0005] of the claim rejections under 35 USC § 103. The structure of Figure 1 wherein R" of unit 1 is

an acetate group, R' of unit III is a sulfate group, and the sulfate group at C-6 of unit V is a hydroxyl group, is the same as pentasaccharide (15) of instant claim 66.

The teachings of Pikas were as disclosed in section [0001] above of the claim rejections under 35 USC § 102.

The teachings of Habuchi *et al.* were as disclosed above in section [0004] of the claim rejections under 35 USC § 103.

The teachings of Nader *et al.* were as disclosed in section [0005] above of the claim rejections under 35 USC § 103.

The teachings of Myette *et al.* were as disclosed above in section [0005] of the claim rejections under 35 USC § 103.

The teachings of Koeller *et al.* were as disclosed above in section [0004] of the claim rejections under 35 USC § 103.

The teachings of Toone *et al.* were as disclosed above in section [0004] of the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of van Boeckel *et al.*, concerning the synthesis of the pentasaccharide sequence DEFGH as an antithrombotic, with the teachings of Kusche *et al.*, regarding the sequence of events involved in the biosynthesis of heparin and heparan sulfate and the various substituents of heparin that are important for antithrombin binding, with the teachings of Pikas, concerning the modification of a polysaccharide having the structure $(GlcA\beta1\text{-}4GlcNAc\alpha1\text{-}4)_n$ by chemical *N*-deacetylation and *N*-sulfation, enzymatic GlcA C5-epimerization, and chemical *O*-

sulfation, with the teachings of Habuchi *et al.*, regarding the availability and substrate specificity of the different enzymes involved in the biosynthesis of heparan sulfate, with the teachings of Nader *et al.*, regarding heparitinase enzymes which are responsible for the degradation of glycosaminoglycans, with the teachings of Myette *et al.*, regarding the substrate specificity of the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, with the teachings of Koeller *et al.*, regarding the use of carbohydrate enzymes as a tool for synthesis of complex carbohydrates, with the teachings of Toone *et al.* regarding enzymes as catalysts in carbohydrate synthesis.

Since van Boeckel *et al.* teach that the pentasaccharide sequence DEFGH is the smallest fragment able to catalyze inhibition of factor Xa and may therefore be useful as an antithrombotic, and Kusche *et al.* teach the importance of the various substituents on the pentasaccharide that are important for antithrombin binding, one of ordinary skill in the art would have been motivated to degrade the polysaccharide chain obtained from *E. coli* K5, as disclosed in Pikas *et al.*, into smaller fragments, more specifically, into the pentasaccharide disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombin III activity. As the teachings of Koeller *et al.* and Toone *et al.* indicate that modification and/or synthesis of carbohydrates are advantageously accomplished by the use of enzymes, one of ordinary skill in the art would have been motivated to look to the different enzymes that could be used in the synthesis of the pentasaccharide fragment. As Toone *et al.* teach that enzymes have chemospecificity, regiospecificity, and stereospecificity, and Kusche *et al.* teach the biosynthetic sequence of events for the synthesis of heparin and heparan sulfate, one of ordinary skill in the art would have

been motivated to model their order of enzymatic synthetic reactions after the biosynthetic pathway, in order to receive the expected benefit that following the biosynthetic sequence would maintain the specificities of the enzymes. However, as the K5 polysaccharide must also be degraded into the pentasaccharide fragment, one of ordinary skill in the art would also have to take into account the substrate specificities of these additional enzymes and insert them appropriately into the reaction scheme so as to maintain specificity of all the enzymes necessary for conversion of the *E. coli* K5 polysaccharide, disclosed by Pikas, into the pentasaccharide sequence disclosed by Kusche *et al.* Since the enzyme specificities for heparitinase, used for degradation of the large polymer into smaller saccharide units, is disclosed by Nader *et al.*, and the enzyme specificities of heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, used for removal of the $\Delta^{4,5}$ unsaturated glycosyl residue resulting from heparitinase digestion, is disclosed by Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to insert their use appropriately into the heparin/heparan sulfate reaction scheme depending on the required substrate specificities of these additional enzymes. More specifically, as Nader *et al.* teach that heparitinase I acts on *N*-acetylated or *N*-sulfated glucosaminido-glucuronic acid linkages of heparan sulfate, one of ordinary skill in the art would have been motivated to insert the use of this enzyme after *N*-deacetylase/*N*-sulfotransferase of the *E. coli* K5 polysaccharide. Another advantage of degrading the polysaccharide early in the synthetic scheme is that smaller fragments are more easily manipulated and characterized than larger structures. With regards to the heparin/heparan sulfate $\Delta^{4,5}$ unsaturated glycuronidase, as Myette *et al.* teach that

this enzyme hydrolyzes the unsaturated $\Delta^{4,5}$ uronic acid at the nonreducing end of oligosaccharides that result from prior heparinase (and heparitinase) eliminative cleavage, one of ordinary skill in the art would have been motivated to insert the use of this enzyme at a point after degradation of the polysaccharide by heparitinase I.

Thus, as the combined teachings of the prior art teach that pentasaccharide DEFGH, as disclosed by van Boeckel *et al.* and Kusche *et al.*, and which is the same as pentasaccharide (15) of the instantly claimed methods, may be useful as an antithrombotic, one of ordinary skill in the art would have been motivated to synthesize such a compound. Since Koeller *et al.* and Toone *et al.* teach that enzymatic reactions of carbohydrates are advantageous over traditional chemical synthetic methods, one of ordinary skill in the art would have been motivated to identify enzymes useful in the synthesis of heparin/heparin sulfate. As Kushe *et al.* disclose the biosynthetic scheme for the synthesis of heparin/heparin sulfate, and the purified enzymes are readily available and their substrate specificities are known, as taught by Habuchi *et al.*, Nader *et al.* and Myette *et al.*, it would have been *prima facie* obvious for one of ordinary skill in the art to use these enzymes, in accordance with their known substrate specificities, to enzymatically synthesize the pentasaccharide sequence disclosed by van Boeckel *et al.* and Kusche *et al.* as having antithrombotic activity. It is noted that several different enzymatic synthetic sequences could result even after taking into account the different substrate specificities of the individual enzymes involved. However, Applicants are requested to note that it has been held that merely reversing the order of steps in a multi-step process is not a patentable modification absent unexpected or unobvious

results. See MPEP § 2144.04. *Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959); *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930); *Cohn v. Comr. Patents*, 251 F. Supp. 437, 148 USPQ 486 (D.C. 1966).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 6, 8, 10, 14 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-26 of copending application no. 10/473,180.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an in vitro method of enriching the portion of anticoagulant active heparin sulfate present in a polysaccharide preparation comprising providing a 3-O-sulfated polysaccharide preparation, and

contacting the preparation with a 6-OST protein in the presence of a sulfate donor (claim 16). The 3-O-sulfated polysaccharide preparation is made in a CHO cell (claim 17).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The unsulfated polysaccharide is isolated from a cell (claim 14).

Thus, the instant claims 1, 2, 6, 8, 10, 14 and 16 are seen to be anticipated by claims 16-26 of copending application no. 10/473,180.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following rejections of record are maintained from the previous Office Action, with modifications made to the rejected claim numbers in view of the allowability of one of the copending applications.

Claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being

unpatentable over claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204,391.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the preparation of *N*-sulfate derivatives of non-sulfated *N*-acetyl heparosan polysaccharides comprising the steps of (a) contacting a non-sulfated *N*-acetyl heparosan polysaccharide witn *N*-deacetylase-*N*-sulfotransferase and glucuronosyl C-5 epimerase to generate an iduronic acid-enriched polysaccharide; (b) contacting the product in (a) with 6-*O*-sulfotransferase and 3-*O*-sulfotransferase; and (c) isolating the product of (b) which yields N-deacetylated N-sulfate derivatives of non-sulfated N-acetyl heparosan (claims 13 and 24). The 3-*O*-sulfotransferase is 3-OST1, 3-OST2, 3-OST3, 3-OST4 or 3-OST5 (claims 18 and 29). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claims 19 and 30).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an N-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon

is a non-sulfated *N*-acetyl heparosan (claim 13). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23, 24 and 26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-O-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30).

Thus, the instant claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 are seen to be anticipated by claims 13, 18, 19, 24, 29 and 30 of copending application no. 11/204,391.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 6, 8, 10-18, 20 and 22-31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 16, 17, 19 and 20 of U.S. Patent No. 7,655,445 (claims refer to U.S. application no. 10/986,058 as the published patent is not immediately available in the database).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the synthesis of an epimerically enriched form of a sulfated heparosan polysaccharide, comprising an acceptor heparosan polysaccharide with PAPS, at least one

sulfotransferase, a p-nitrophenyl sulfate donor, an arylsulfatase and an epimerase (claim 1). The epimerase is a glucuronosyl C5 epimerase (claim 6). The sulfated heparosan is isolated (claims 16). The sulfotransferase is an *N*-deacetylase-*N*-sulfotransferase, heparin sulfate 2-*O*-sulfotransferase, 6-*O*-sulfotransferase, 3-*O*-sulfotransferase, 2-*O*-sulfotransferase, or a combination thereof (claim 17). The 3-*O*-sulfotransferse is 3-OST1 (claim 19). The 6-*O*-sulfotransferase is 6-OST1, 6-OST2 or 6-OST3 (claim 20).

The claims of the instant application are drawn to a method of preparing a sulfated polysaccharide or heparan sulfate comprising treating an unsulfated or incompletely sulfated polysaccharide or unsulfated heparan synthon with at least one enzyme (claims 1, 2, 8 and 10). The enzyme is selected from the group consisting of an *N*-deacetylase, an *N*-sulfotransferase, an epimerase and an *O*-sulfotransferase (claim 6). The method comprises (a) treating an unsulfated polysaccharide with an *N*-deacetylating reagent; (b) treating the step (a) product with an *N*-sulfating reagent; (c) treating the step (b) product with an epimerizing reagent; and (d) treating the step (c) product with at least one *O*-sulfating reagent (claims 11 and 12). The heparan synthon is a non-sulfated *N*-acetyl heparosan (claim 13). The unsulfated polysaccharide or heparan synthon is isolated from a cell or *E. coli* bacteria (claims 14-17). The deacetylating reagent is selected from the group consisting of a deacetylase and *N*-deacetylase-*N*-sulfotransferase (claims 18 and 20). The epimerizing reagent is selected from the group consisting of C5-epimerase (claim 22). The *O*-sulfating reagent incorporates a 2-*O*-sulfate group, 3-*O*-sulfate group or a 6-*O*-sulfate group (claims 23-

26). The *O*-sulfating reagent is a 3-*O*-sulfotransferase selected from the group consisting of 3-OST1, 3-OST2, 3-OST3, 3-OST4, 3-OST5 and 3-OST6 (claims 27 and 28). The *O*-sulfating reagent is a 6-*O*-sulfotransferase selected from the group consisting of 6-OST1, 6-OST2 and 6-OST3 (claims 29 and 30). The *O*-sulfating reagent is a 2-*O*-sulfotransferase (claim 31).

Thus, the instant claims 1, 2, 6, 8, 10-18, 20 and 22-31 are seen to be anticipated by claims 1, 6, 16, 17, 19 and 20 of copending application no. 10/986,058, now U.S. Patent No. 7,655,445.

Response to Arguments

Applicants note that they disagree with the obviousness-type double-patenting rejections, but request that the provisional rejections be held in abeyance until allowable subject matter has been identified, at which time they will consider filing a Terminal Disclaimer. Applicants' request is acknowledged. However, Applicants are requested to note that copending U.S. application no. 10/986,058 has been allowed as U.S. Patent No. 7,655,445, and thus this rejection is no longer considered provisional.

The rejections are still deemed proper and therefore maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
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